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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,705	09/11/2003	A. Thomas Look	112706.123US2	6046

24395 7590 11/22/2006

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,705	LOOK ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *3,25-30,38 and 60-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,4-24,31-37,39-59 and 67-74* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02/24/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group I in the reply filed on 08/18/2006 is acknowledged. The traversal is on the ground(s) that the groups are classified together and are both drawn to novel transgenic fish comprising an oncogene operably linked to a promoter and methods of using the fish. This is not found persuasive because the transgenic fish are patentably distinct and comprise structurally and functionally distinct transgenes. The fish of Group II does not express the claimed oncogene without introduction of a site-specific recombinase. This is not the case for the fish of Group I that express the oncogene under the direction of a tissue specific promoter, not part of the fish of Group II. The fish of the different groups are structurally distinct, require different method steps for use and require distinctly different mechanisms of gene regulation that are distinct in the art. Therefore, this aspect of the restriction requirement is maintained.

Applicant also traverses the species restrictions stating that it would not require serious burden on the examiner to examine each of the promoter species together. This argument is not persuasive because each promoter is distinct in the art and would require separate search. Furthermore, the species restriction is not made on the sole basis of search burden. Each fish comprising a different promoter-transgene construct is a patentably distinct fish with different phenotype, function and use. As set forth in the office action below, each different promoter, even those specific to the same cell or tissue types requires special consideration with respect to the levels of expression and phenotypic effects. Therefore, this aspect of the restriction is maintained as well.

The requirement is still deemed proper and is therefore made FINAL.

Claim 1-74 are pending. Claims 25-30 and 60-66 are withdrawn as being drawn to a nonelected invention. Claims 3 and 38 withdrawn as being drawn to non-elected species. Claims 1,2,4-24,31-37, 39-59 and 67-74 are under consideration in the instant office action.

Specification

The disclosure is objected to because of the following informalities:

The Brief Description of Figure 13 is not in accordance with MPEP 608.01(f), which states:

> The examiner should see to it that the figures are correctly described in the brief description of the drawing, that all section lines used are referred to, and that all needed section lines are used. If a figure contains several parts, for example, figure 1A, 1B, and 1C, the figure may be described as figure 1. If only figure 1A is described in the brief description, the examiner should object to the brief description, and require applicant to either add a brief description of figure 1B and 1C or describe the figure as "figure 1."

The description of Figure 13 refers to Figure 13A-C but fails to refer to figure 13D.

Appropriate correction is required.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1,2,4-24,31-37, 39-59 and 67-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a transgenic fish whose genome comprises a transgene comprising a cMyc gene operably linked to the Rag2 promoter wherein cMyc is expressed in T-lymphocytes of the fish resulting in cMyc-induced T-cell lymphoblastic leukemia and 2) a method of screening drugs or agents that mediate cMyc-induced T-cell lymphoblastic leukemia comprising contacting a first of said transgenic fish with a test drug or agent and comparing said contacted fish with a second, control transgenic fish that is not contacted with said drug or agent, wherein a decrease in cMyc-induced lymphoblastic leukemia in the contacted fish compared to the control fish indicates a potential drug or agent for decreasing cMyc-mediated T-cell lymphoblastic leukemia, does not reasonably provide enablement for 1) a transgenic fish whose genome comprises any oncogene operably linked to any promoter wherein the oncogene is not expressed and does not cause an oncogenic phenotype or 2) a

method of using said fish as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are broadly drawn to a transgenic fish comprising a transgene encoding any oncogene operably linked to any promoter. Dependent claims limit the genera of promoters and oncogenes, for example to T-cell specific promoters, or in the case of claim 8, specifically to the RAG2 promoter. Other claims limit the oncogene; claim 11, for example, being limited to a T-cell oncogene. Other claims require a reporter gene be fused to the oncogene of the transgene construct (claims 19-23). Claims 24 and 35 are drawn specifically to a transgenic fish whose genome comprises a cMYC gene operably linked to a RAG2 promoter; however, the claims fail to require that the cMYC gene be expressed or cause any phenotype. Claims 36,37,39-59 and 67-74 are drawn to screening methods using the claimed fish. In

addition to the breadth set forth for the fish, above, the method claims broadly encompass any methodology of determining if a drug or agent modulates oncogene mediated neoplastic transformation and does not require any type of comparison to the an untreated control fish.

The specification has taught generating transient transfected and germline transgenic zebrafish expressing a mcMYC transgene operably linked to the zebrafish Rag2 promoter, in T-cells. mcMYC, EGFP-mcMYC, and MYC-ER (page 41, paragraph 2), constructs were used in independent experiments. All constructs led to leukemic phenotypes in the fish, including the MYC-ER construct in the absence of tamoxifen, albeit at a lower frequency. The specification has not taught the genus of transgenic fish encompassed by the claims or methods of using them. Examples 3-5 provide prophetic teachings of developing other transgenic fish models of cancers. However, the specification does not provide the guidance necessary to make any transgenic fish expressing any oncogene other than cMYC under the control of the RAG2 promoter, in detail sufficient enough to overcome the unpredictability that is well-established in the art of making transgenic animals.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. The art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene [Wall, 1996 **Theriogenology**, 45:57-68]. The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, **J. Biotech.** 34:269-287, specifically page 273-276). The leakiness of the ER/tamoxifen control system in the instant invention is an example of this unpredictability (see page 52, last paragraph). Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron, 1997, **Molec. Biol.** 7, pages 253-265,

specifically page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron, page 256, lines 3-9). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann, 1997, **Transg. Res.** 7,:73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). Wall et al. also highlights that combining disparate DNA sequences in transgenic animals is more guesswork than science and is not predictable even based on in vitro activity of a construct [**Journal of Andrology**, 18:236-239, 1997, specifically, p. 237, col. 1, last paragraph]

The art at the time of filing with respect to transgenic fish was that promoters of heterologous origin were not efficiently or effectively expressed (refer to Udvadia, 2003, Dev. Biol. Vol. 256, page 7, col.1, paragraph. 4). In fact, it is thought that non-fish promoters are often silenced when introduced into the genome of zebrafish [see Higashijima, 1997, **Dev. Biol.,** 192 :289-299]. Higashijima found that use of zebrafish derived promoters in zebrafish resulted in much more consistent expression with higher fidelity across a large number of independently derived lines (refer to paragraph bridging col. 1-2 of page 297). Notably, all-fish derived transgenes using fish promoters are often not expressed as exemplified in the instant invention (page 51, lines 18-20). Therefore, it was recognized in the art that use of heterologous promoters in fish was highly unpredictable as to whether the transgene would be expressed, silenced, or expressed to a particular level and in a specific desired pattern.

Thus the state of the art held, for diverse species including fish, that the activity of a promoter and the level of expression obtained was highly unpredictable and is dependent on numerous factors including the gene of interest linked to the promoter, the characteristics of the promoter itself, the relationship between the species from which the promoter was derived and the species in which it is being used, the site of integration as well as how tightly regulated the promoter is. The contribution of each of these

factors to the activity of a transgene in the claimed fish cannot be determined in such a way as to overcome the unpredictability established in the art with respect to how much transgene product will be expressed and what phenotype that level of expression will cause. The specification has not provided the guidance necessary to overcome this unpredictability such that one can know which fish encompassed by the claims will exhibit a phenotype and what use that phenotype will have.

The functional activity and phenotypic effect of ectopically expressed transgenes was also unpredictable. The in vivo activity of an endogenous gene is not always an indicative of the phenotypic effect that ectopic expression will bring. In some instances, overexpression of a gene may unexpectedly have no effect or it may have highly unpredicted and surprising effects. While unpredictability lies in large part due to the level of expression (see Wall, 1997), even at a well-controlled level, the effect on phenotype of an ectopically expressed protein is highly unpredictable and cannot be determined without making the animal in question. With this in mind, it would not have been predictable at the time of filing, given the guidance in the specification, what phenotypic effect any of the claimed transgenes would have other than the expression of cMYC under the control of the RAG2 promoter as taught by the specification.

Therefore, it would require an undue experimentation to carry out the invention as broadly claimed with any promoter and any oncogene as claimed.

Other than the exemplified transgenic mouse, it would have required undue experimentation to predict the results achieved in any single host fish comprising and expressing any oncogene, the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype.

The claims also fail to require that the transgene be expressed or cause an effect on the phenotype of the fish. Without expression of the transgene, claims encompass mere possession of a transgene within the genome. With the exception of causing a gene disruption, which is not the object of this invention, a fish possessing but not expressing a transgene would not have a phenotype. The specification teaches how

to use the claimed fish with a leukemic phenotype. In the absence of a phenotypic requirement, one of skill in the art would not know how to use the claimed fish.

The claimed methods are broadly drawn to screening for drugs or agents that modulate, either positively or negatively, oncogene-mediated neoplastic or hyperplastic transformation. The specification, however, does not teach how to use the claim method that would positively modulate, increase, neoplastic transformation. A use for such a screen is not readily apparent. Furthermore, the claims fail to require any sort of comparison for determining whether a change has occurred. The claims encompass treatment of a fish to determine whether the agent, for example, decreases expression of leukemic markers or number of tumors. This cannot be done without a control for comparison. The claim encompasses use of a single fish comprising the claimed transgene discussed above. However, the claims do not require that the fish exhibit any cancer-related phenotypes. The specification teaches that of 350 F_0 founder fish, only 7 were germline transgenic and only one of those expressed the transgene. One of skill in the art would not know how to carry out the claimed method of using a fish whose genome comprises the transgene but does not express it. The specification does not clearly establish that all of the stable germline transgenic offspring will develop tumors, however, this is assumed to be the case for both homozygotes and heterozygotes given that no fish appear to survive to mating age to propagate the line (page 52, lines 6-17). Thus, it appears that the claimed method should require an untreated sibling control as a means of comparison for determining the effect of an agent or drug in the claimed method of screening.

With respect to including necessary method steps for determining a change iresulting from a drug or agent, Applicant should take care not to introduce new matter and to point to the specification for relevant support of any amendments to the claims.

Written Description

Claims 18 and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The specification has described the MYC gene and the art has established functional conservation of MYC homologues in sufficient detail. The specification, however, has not described an oncogene substantially similar to cMYC in terms of its structural or functional identity. In fact, the specification has not set forth any definition of what is intended by the terminology "substantially similar to".

In the instant case the MYC variants encompassed by the claims lack a written description. The specification fails to describe what DNA molecules fall into this genus and it was unknown as of Applicants' effective filing date that any of these DNA molecules would have the property of encoding a MYC polypeptide having the same structural and functional properties as that encoded by mouse cMYC. The claimed embodiments of MYC variants encompassed within the genus lack a written description. There is no evidence on the record of a relationship between the structures of the nucleotide sequences coding for the MYC variants and the nucleotide sequence encoding mouse cMYC that would provide any reliable information about the structure of DNA molecules within the genus. The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification and that is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such

that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641,1646 (1998).

With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides or polypeptides, and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid molecules and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by any member of the genus of genes substantially similar to MYC encompassed by the claims. Therefore, corresponding homologues, but not the full breadth of the claims encompassing genes substantially similar thereto, meet the written description provision of 35 U.S.C. §112, first paragraph. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that "to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude "the inventor invented the claimed invention".

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18 and 53 are vague and indefinite because the limitation "substantially similar" is conditional and no single set of defining conditions has been recited in the claim or the instant specification. The claim is not just broad by the use of the term but is indefinite because it is not known what is intended to be encompassed by the claim because no definition of "substantially similar" is set forth and the metes and bounds cannot be determined.

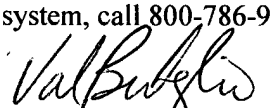
Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Valarie Bertoglio
Examiner
Art Unit 1632